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Supercomputing Drug Screening For Deadly Heart Arrhythmias

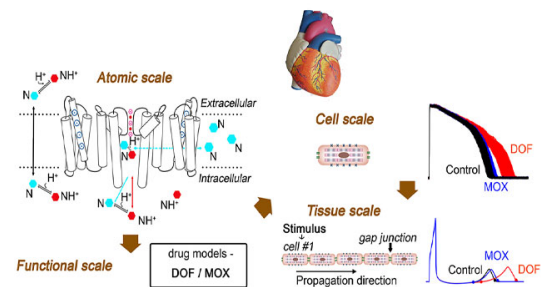
UC Davis researchers use computational pipeline to develop cardiotoxicity tests

Death from sudden cardiac arrest makes headlines when it strikes athletes. But it also causes the most deaths by natural causes in the U.S., estimated at 325,000 per year.

According to the Cleveland Clinic, the heart's bioelectrical system goes haywire during arrest. The malfunction can send heartbeats racing out of control, cutting off blood to the body and brain. This differs from a heart attack, which is caused by a blockage of the heart's arteries. The leading risk factors for sudden cardiac arrest are a past attack and the presence of disease. Another risk factor is the side effects from medications, which can cause deadly arrhythmias.

Using supercomputers, scientists have developed for the first time a way to screen drugs through their chemical structures for induced arrhythmias.

“What we set out to do was to try to solve that problem by building a computer-based pipeline for screening,” said Colleen Clancy, a professor in the Department of Physiology and Membrane Biology and the Department of Pharmacology at the UC Davis School of Medicine. Clancy co-authored a study on the computational cardiotoxicity drug screening pipeline in the journal *Circulation Research* in April 2020.



*A computational pipeline to screen drugs for cardiotoxicity has been developed with the use of supercomputers. The pipeline connects atomistic scale information to protein, cell, and tissue scales by predicting drug-binding affinities and rates from simulation of hERG ion channel and drug structure interactions. These values are used to model drug effects on the hERG ion channel function and an emergent cardiac electrical activity alteration. Credit: Yang et al., *Circulation Research**

“The major novelty of the pipeline is that we found a way to connect the atomistic scale to higher level function scales, like protein function, cell function, and in our simulated tissue-level models we can calculate the spatial and temporal gradients of electrical activity in those simulated pieces of tissue,” Clancy said. “That is an approximation of the electrocardiogram that’s measured in the clinic. We can do a direct comparison between the electrocardiogram in the simulated tissue, and electrocardiograms from patients that have taken those drugs.”

Up until the early 2000s, the reason most drugs were removed from the market following FDA approval was cardiotoxicity in the form of deadly arrhythmia. In 2005, the FDA required a separate test for all drugs. It measured the average time between the Q and T waves on an electrocardiogram, a record of the heartbeat. QT prolongation became a red flag for drug cardiotoxicity. But one problem is that some harmless substances, like grapefruit juice, also prolong QT interval, and using it as a proxy for heart arrhythmia could mean the loss of potentially useful and safe drugs.

The two drugs chosen in the study both prolonged the QT interval. One of them, dofetilide, is a known proarrhythmic agent. The other, moxifloxacin, has a strong safety profile in healthy humans. “There’s been no way to distinguish between those two classes,” said Clancy. “That’s what we were able to show in the computational pipeline.”

Starting from the chemistry of the drug interactions with a target, the scientists used that information to predict proarrhythmia vulnerability through a machine learning approach based on multi-scale computer simulation data.

Clancy and colleagues chose the hERG (human Ether-à-go-go-Related Gene) potassium channel in the heart as the drug target in the first step of their computational pipeline. The hERG mediates the electrical activity of the heart, and drug companies usually screen for whether a drug blocks it.

"The big challenge computationally is the system that we studied is pretty large," said study co-author Igor Vorobyov, an assistant professor in the Department of Physiology and Membrane Biology and the Department of Pharmacology at the UC Davis School of Medicine. "It's on the atomistic scale. We have around 130,000 atoms in our system. This includes the hERG protein embedded in the lipid membrane surrounded in a salt aqueous solution in water."

The calculations involved billions of individual time steps to achieve an all-atom simulation of several microseconds, enough to get detailed information on how the drug binds to the target. “Here is where supercomputers come in very handy,” said Vorobyov.

Researchers were awarded time on the *Stampede2* system at the Texas Advanced Computing Center (TACC), as well as *Comet* at the San Diego Supercomputer Center (SDSC), making use of *Comet*'s GPU and CPU nodes. The National Center for Supercomputing Applications (NCSA) allocated use of its National Science Foundation-funded *Blue Waters* system. For long-term (greater than 5 microsecond) simulations of the relatively slow entry of the drug into cardiac cells, the scientists also made use of *Anton 2*, a special-purpose supercomputer for biomolecular simulation designed and constructed by D. E. Shaw Research (DESRES) and hosted by Pittsburgh Supercomputing Center (PSC).

The team used enhanced sampling simulations, called umbrella sampling, to facilitate the molecular dynamics simulations and yield quantitative determination of the binding affinities and rates of reaction needed for linking scales and feeding parameters further up the pipeline to the functional model.

“That was the novel linkage between our scales that we’ve both worked on for many years,” added Clancy. “Until now, there was no way to really connect those scales in a meaningful way.”

The researchers are taking the next steps in their computational pipeline to expand the set of drugs screened for cardiotoxicity, by looking at a variety of agents that have been part of the Comprehensive In Vitro Proarrhythmia Assay (CiPA) safety pharmacology testing group. They’re also working with the biopharmaceutical company Amgen to get blinded compounds for their screening.

“The idea is that Amgen would give us the chemical structures of the drugs, but we wouldn’t know whether they were proarrhythmic or not,” said Clancy. “Then we’ll use the pipeline to make some predictions about those drugs, and send those results back where they will reveal if our model was accurate in predicting what they’ve seen.”

Clancy and the team also want to move the research into a personalized medicine approach, building models of an individual’s cellular electrophysiology that include some genetic background. One project cultures heart muscle cells from individuals to develop a model called the ‘induced pluripotent stem cell-derived cardiac myocyte.’

"The benefit of a personalized medicine approach is that it includes all of the genetic information in the background, so one can screen drugs and then start to ask why some individuals are susceptible to drugs and proarrhythmia from drugs, while other people aren't," said Clancy. "We may even be able to work toward developing reconstructions of their hearts in silico."

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